Is industry influencing carcinogen assessments in the USA?

Chemical manufacturers and some US lawmakers are demanding dramatic reforms and increased external scrutiny of the Environmental Protection Agency's (EPA's) chemical carcinogenicity and toxicity assessment programme, known as the Integrated Risk Information System (IRIS), but these would hinder identification of chemical threats to public health, IRIS proponents told *The Lancet Oncology*.

IRIS assessments "create public confusion, unwarranted alarm and unnecessary litigation", testified Calvin Dooley (American Chemistry Council, Washington, DC, USA) at a July 14, 2011, hearing of the congressional Investigations and Oversight Committee. Dooley called for National Academy of Sciences (NAS) reviews of all IRIS draft assessments and a "comprehensive overhaul" of the entire programme. EPA has dragged its feet in responding to congressional inquiries about IRIS, according to Texas Representative Paul Broun, who chairs the Investigations and Oversight Committee.

EPA has announced internal reforms, including the creation of a standing IRIS Advisory Committee that would examine decisions about which studies are included or excluded from IRIS assessments. But the agency is resisting calls for routine external reviews by the NAS and White House.

External reviews by the White House, NASA, and Pentagon effectively halted IRIS's release of new chemical assessments during the Bush administration. The Pentagon and NASA delayed IRIS assessments of "mission critical" jet and rocket fuel components for nearly a decade, for example. The US Government Accountability Office concluded in 2008 that the IRIS database was at "serious risk" of becoming obsolete as a result of such delays.

IRIS provides the world's only centralised, independent database of quantitative chemical risk assessments, which are used by regulatory agencies around the world to limit occupational and consumer exposures and to trigger environmental clean-ups, noted Jennifer Sass of the Natural Resources Defence Council (NRDC, Washington DC, USA).

"The International Agency for Research on Cancer [IARC] also does chemical assessments, but IRIS does cancer and non-cancer endpoints and is such a lightning rod because it provides quantitative risk estimates that can be used for regulatory exposure limits", says Sass. Whereas IARC qualitatively groups chemicals as "not classifiable", "probably not carcinogenic to humans", "possibly" or "probably" carcinogenic to humans, or "carcinogenic to humans", for example, IRIS risk assessments provide quantitative reference doses—numbers against which regulators can weigh relative health risks against cleanup or other economic costs. Delays have been "completely political, putting profits before health", says Sass.

EPA Administrator Lisa Jackson announced plans to kick-start IRIS assessments in May, 2009, including plans to finalise and release long-stalled assessments of economically important compounds like formaldehyde, which a draft IRIS assessment had established to be a human carcinogen tied to nose and throat cancers and myeloid leukaemias. But at the urging of the industry-funded Formaldehyde Council, Louisiana Senator David Vitter blocked confirmation of Paul Anastas (President Obama's nominee for director of the EPA Office of Research and Development, which oversees IRIS) until EPA agreed to submit its formaldehyde assessment to the NAS for external review.

The NAS review, released in April, 2011, takes the EPA to task for unclear rationales related to its conclusions and for failing to fully explain why certain studies are used in IRIS assessments whereas others are not. Although supportive of IRIS's decision to include leukaemia studies in its formaldehyde review, the NAS questioned the conclusion that this chemical is a leukaemogen, in view of the lack of clear biomolecular carcinogenic pathways.

"I think the NAS was a little bold in saying that", says Sass. "We don't understand the mechanisms for most cancers. These were robust studies of tens of thousands of workers, done by the US National Institute of Occupational Safety and Health."

EPA voluntarily postponed its release of new risk assessments for the plastic additive acrylonitrile and fuel additives methyl tertiary butyl ether (MTBE) and ethyl tert-butyl ether (ETBE), after questions arose about the results from animal cancer studies of methanol done at the Ramazzini Institute, Bologna, Italy. IRIS had relied in part on the Ramazzini studies in its acrylonitrile, MTBE, and ETBE assessments (Defense Environment Alert, July 5, 2011).

The agency announced in July that it will now abandon safety factors from carcinogenicity estimates for acrylonitrile based on those studies, dramatically reducing the stringency of anticipated exposure limits and environmental clean-up requirements (Risk Policy Report, July 5, 2011). Acrylonitrile is ubiquitous in consumer products and waste dumps; it is used in making plastics, synthetic rubber and surface coatings, adhesives, and medical tubing.

Despite setbacks, IRIS is scheduled to complete ten risk assessments by next summer, including tetrachloroethylene, arsenic, chromium VI, platinum salts, and trichloroethylene, and is considering assessments of manganese, ammonia, ethylbenzene, ethanol, and other suspected carcinogens.

IRIS is not alone in provoking industry ire. The industry-funded Styrene Information and Research Center (SIRC, Washington, DC, USA) unsuccessfully sought a judge's order in July, 2011, to remove styrene from the US Health and Human Services Department's National Toxicology Program's (NTP's) report on

For more on the **Defense Environment Alert** see http://environmentalnewsstand.com/Defense-Environment-Alert/Defense-Environment-Alert-07/05/2011/menu-id-307.html

For the **Risk Policy Report** see http://environmentalnewsstand.com/Risk-Policy-Report/Risk-Policy-Report-07/05/2011/menu-id-306.html

For more on **jet and rocket fuel components** see News *Lancet Oncol* 2008; **9**: 518

For more on the **NAS review** see http://dels.nas.edu/Report/Review-Environmental-Protection-Agency/13142

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For the **NTP report** see http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf

carcinogens. "NTP is under very serious assault [from the chemical industry]", says Sass.

The NTP suffers systemic "process shortcomings" and ignored a "principal" SIRC-funded review of styrene carcinogenicity when making its determination that styrene is "reasonably anticipated" to be a human carcinogen, SIRC's Joe Walker told *The Lancet Oncology*.

But such objections are really part of industry's "delay-game" strategy to postpone regulations, says Sass. The styrene and formaldehyde assessments are case studies in how chemical manufacturers, polluters, and industry consultants like SIRC, use every tool at their disposal to delay release of final assessments of chemicals' health risks, concludes Sass.

Bryant Furlow

3rd congress of the International Academy of Oral Oncology

The 3rd congress of the International Academy of Oral Oncology was held on July 14–17, 2011, in Singapore

Palliative radiotherapy

Sushmita Ghoshal (Chandigarh, India) and colleagues presented results of a prospective study comparing the palliation achieved with a 2-day so-called Quad shot radiotherapy regimen to a standard 2-week treatment. 50 patients with stage IV head and neck cancer were randomly assigned to receive either Quad shot palliation treatment (14 Gy in four fractions over 2 days) or standard palliation (30 Gy in ten fractions over 2 weeks). Quality of life (QOL) before and after treatment was assessed using the Washington University questionnaire. Pain relief, swelling, dysphagia, and hoarseness was 62%, 86%, 40%, and 63% for the Quad shot group versus 77%, 91%, 50%, and 54% for standard palliation, respectively. QOL improved in both arms with no statistical difference. With median overall survival of 5 months for the patients receiving Quad shot palliation versus 6 months for those receiving standard treatment, the 2-day Quad shot treatment could be a suitable option for palliative radiotherapy in rural or remote areas.

Circulating tumour cells

Marco Blessmann (Hamburg, Germany) and colleagues assessed the prognostic significance of circulating tumour cells (CTC) in the bone marrow and peripheral blood in patients with oral squamous-cell carcinoma. 90 patients with histologically diagnosed oral squamous-cell carcinoma, who underwent primary surgical treatment and subsequent radiotherapy or chemotherapy, were followed up for 36 months. The presence of CTC was significantly associated with the presence of distant metastases ($p<0·0001$), and with relapse ($p=0·0007$). Although preliminary, these results suggest that CTC in peripheral blood or bone marrow could be a marker of patients with oral squamous-cell carcinoma at high risk of metastases and recurrence.

Lymph-node-metastasis gene expression signature

The assessment and treatment of regional lymph nodes in the neck of patients with squamous-cell carcinoma of the head and neck is the subject of much debate. Frank Leusink (Utrecht, Netherlands) and colleagues presented the validation study of a lymph-node-metastasis gene expression signature to discriminate metastasising from non-metastasising disease. Gene expression was analysed using a DNA microarray that included 696 previously reported predictive genes. The negative predictive value of the signature was assessed on the whole multicentre cohort (n=222), on clinically node negative (cN0) tumours (n=143), and on T1 and T2,cN0 oral cavity squamous-cell carcinoma samples (n=101). The negative predictive value of the gene signature was 72% overall, 85% for the cN0 subset, and 89% for the T1 and T2,cN0 group.

Concurrent chemoradiotherapy with capecitabine and oxaliplatin

Dauren Adilbay (Almaty, Kazakhstan) and colleagues presented results of a phase 2 study assessing the efficacy and safety of concurrent chemoradiotherapy with capecitabine and oxaliplatin in patients with locally advanced squamous-cell carcinoma of the head and neck. 36 patients with stage III or IV disease received two cycles of intravenous oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 2000 mg/m^2 daily from day 1 to day 14 at 3-week intervals. The treatment was found to be well-tolerated and effective with 63% of patients achieving a complete response, 37% achieving a partial response, and a 2-year overall survival of 75%.

Predicting long-term survival for tongue-base cancer

The treatment of squamous-cell carcinoma of the tongue-base has evolved from surgery and radiotherapy towards concomitant chemoradiation. Richard Nason (Manitoba, Canada) and colleagues presented results from a historical cohort of 290 patients with advanced cancer of the base of the tongue—followed prospectively—to assess 10-year treatment outcomes over the time that the pattern of treatment was changing. Multivariate models showed an independent effect of stage, sex, age, and initial treatment modality on overall survival. Treatment with radiotherapy and chemotherapy reduced the risk of death over 10 years by 89% (HR 0·11, 95%CI 0·1–0·2; $p<0·0001$) and surgery plus radiotherapy reduced the risk of death over 10 years by 87% (HR 0·13, 95%CI 0·1–0·2, $p<0·0001$).

Audrey Ceschia

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